

## **PSEUDO HYPOPARATHYROIDISM PRESENTING WITH REFRACTORY**

### **SEIZURES: AN INTERESTING REPORT OF 3 CASES**

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#### **ABSTRACT**

In patients presenting with refractory seizures every effort must be made to rule out potentially treatable causes to avoid prolonged usage of antiepileptic drugs. Here we report three interesting cases presenting with refractory seizures who had intracranial calcifications in their CT scans and on biochemical investigations were found to have hypocalcemia with pseudohypoparathyroidism. All patients had a good response to treatment with calcium, vitamin D supplementation along with antiepileptic drugs

**KEYWORDS:** Seizures, Pseudohypoparathyroidism, Basal Ganglia Calcification, Hypocalcemia

#### **INTRODUCTION**

Hypocalcemia caused by a variety of disorders is one of the treatable causes of recurrent seizures. There are very few reported cases in literature of pseudohypoparathyroidism (PHP) with hypocalcemia, intracranial calcification and seizures (2,3,4). We present clinical and radiological profile of 3 patients who presented with seizure disorder and turned out to be cases of pseudohypoparathyroidism with hypocalcemia. The finding of intracranial calcifications on CT Brain and abnormalities in further metabolic investigations led to diagnosis and specific treatment in these cases.

#### **MATERIALS AND METHODS**

We describe 3 unrelated patients with complaints of refractory seizures and intracranial (including basal ganglia) calcifications on CT Brain.

#### **OBSERVATIONS**

##### **Case 1**

A 14 year old boy born of a non-consanguineous marriage delivered by caesarian section, normal developmental history, presented with complaints of intermittent tetanic posturing of limbs since 1.5 years and partial with secondary generalized seizures since 8 months. On examination vitals were normal and no focal neurological deficit was seen. Trousseau and Chvostek signs were positive on examination. Suspecting on the lines of hypocalcemia with seizure disorder patient was investigated and following were the findings- Hemoglobin (Hb) – 12.9 gm%; Total leucocyte count (TLC) – 6,900/ cmm; Differential leucocyte count (DLC) – N63L35E1B1; Total serum calcium 4.2 mg/dl (normal range – 8.7 – 10.2 mg/dl) with ionized fraction of 2.3 mg/dl (normal range – 4.5 – 5.3 mg/dl); serum phosphorous- 9.4mg/dl (2.5 – 4.3mg/dl); serum parathyroid hormone (PTH) – 342 pg/ml (normal range 8-51 pg/ml); serum magnesium – 2 mg/dl (normal range – 1.5 – 2.3 mg/dl); Alkaline phosphatase – 1046 IU/L ( normal range – 20 – 140 IU/ L); Liver function test (LFT) and renal function test (RFT) were within normal limits; thyroid profile – normal; X-ray wrist and hand was

normal; electroencephalogram (EEG) showed background slowing along with focal and generalized sharp wave discharges; USG abdomen – normal; CT Brain was suggestive of symmetrical calcification in bilateral basal ganglia, subcortical region and cerebellum (**see figure 1**). Patient was diagnosed as a case of PHP without Albright's hereditary osteodystrophy (AHO) phenotype and was treated with calcium and vitamin D supplementation along with antiepileptic drugs.

## Case 2

An 11 year old boy born of a non-consanguineous marriage delivered by normal vaginal route, normal developmental history, presented with complaints of partial with secondary generalized seizures since 2 years duration. On examination vitals were normal and he had a round looking face (**see figure 2**) and no focal neurological deficit was seen. Trousseau sign and Chvostek signs were positive on examination. On investigation, Hb - 13.6 gm/dl. TLC 6500/cmm, DLC- N69L26E4B1; Total S. Calcium 4.0 mg/dl, S. Phosphorous - 8.3mg/dl, PTH – 276 pg/ml, S. Magnesium – 2.2 mg/dl; Alkaline phosphatase – 1548 IU/L; LFT and RFT were within normal limits; thyroid profile – normal; X-ray wrist and hand – suggestive of osteopenia and small 4<sup>th</sup> and 5<sup>th</sup> metacarpals (**see figure 3**); USG abdomen - normal; EEG showed slowing of background along with focal and generalized sharp wave discharges; CT Brain was suggestive of bilateral extensive symmetrical basal ganglia and subcortical Frontal and Parietal calcifications (**see figure 4**). Patient was diagnosed as a case of PHP with Albright's hereditary osteodystrophy (AHO) phenotype 1a and was treated with calcium and vitamin D supplementation along with antiepileptic drugs.

## Case 3

A 5.5 years old girl child born of a non-consanguineous marriage delivered by caesarian section, no perinatal insult, with developmental delay (walking 1.5 year, bisyllable speech 2.5 years) presented with complaints of partial with secondary generalized seizures since 1 month duration. On examination vitals were normal and she had a round looking face (**see figure 5**) and no focal neurological deficit was seen. Trousseau and Chvostek signs were positive on examination. On investigation, Hb- 11.6 gm/dl; TLC 8300/cmm; DLC- N62L29E7B2; Total S. Calcium 4.6 mg/dl, S. Phosphorous- 10.6 mg/dl, S. Magnesium – 1.8 mg/ dl; PTH – 712 pg/ml; Alkaline phosphatase – 1059 IU/L; LFT and RFT were within normal limits; X-ray wrist and hand – s/o osteopenia and small 4<sup>th</sup> and 5<sup>th</sup> metacarpals ; thyroid profile – normal; USG abdomen - normal; ; CT Brain was suggestive of bilateral extensive symmetrical basal ganglia and subcortical Frontal calcifications (**see figure 6**). Patient was diagnosed as a case of PHP with AHO phenotype 1a and was treated with calcium and vitamin D supplementation along with antiepileptic drugs.

## RESULTS

All 3 patients were initially refractory to antiepileptic drugs. After being fully investigated, they were given IV calcium initially and then maintained on oral calcium (1 -1.5 gm/day) and vitamin D (0.50 µg/day) along with the antiepileptics and showed remarkable response. After 3 months of starting treatment all 3 patients had normal serum calcium and phosphorus levels. None of them developed seizures again after being treated for hypocalcemia. The anticonvulsants were withdrawn in one patient while they are in the process of being tapered off in the other 2 patients. All 3 are maintained on vitamin D (0.25µg/day) and oral calcium (1 gm/ day ).

## DISCUSSIONS

Pseudohypoparathyroidism (PHP) is a hereditary disorder characterized by symptoms and signs of hypoparathyroidism in association with distinctive skeletal and developmental defects. The symptoms and signs of hypocalcemia develop in childhood. The average age at the onset of symptoms is 8 years, although the diagnosis is not made in some relatively asymptomatic persons. The presenting symptoms are tetany and less often seizures(1). There is paucity of reported cases of PHP presenting as seizures in the literature. Although children are commonly affected (2) but some asymptomatic patients may be detected later and occasionally the seizures may be resistant to treatment (3). Seizures of a wide variety occur. Although generalized tonic-clonic seizures are most typical, focal motor seizures with or without secondarily generalization are also common (4). The universal feature of seizures in nearly all PHP patients have been their poor response to anticonvulsants but their excellent and rapid control without medication once serum calcium levels have been restored to normal, as was seen in our cases. Hence hypocalcemia must be ruled out in any patient with seizures resistant to anticonvulsants. There is no fixed level of hypocalcemia at which seizures will occur (4).

The interictal EEG reflects the effect of hypocalcemia on neuronal function, and in severe cases (i.e., serum calcium <5-6 mg/dl) it typically shows generalized slowing of the background, with paroxysmal bursts of delta waves, sharp waves, or sharp wave – slow wave complexes often exacerbated by hyperventilation (4,5).

The pathogenesis of cerebral calcification and the role it plays in causing seizures remains unclear (4,6). Anoxia may explain the distribution of calcification in boundary zones of major territorial arteries and in the production of abnormal vascular permeability and deposition of calcium salts in selective regions (6). The most unclear facts are that cerebral calcifications are bilateral and symmetrical and usually do not correspond in location to focal seizures and that correction of hypocalcemia eliminates seizures without any change in intracerebral calcifications (4) as was seen in our cases. A generalized disturbance of calcium and phosphorus metabolism, however important it may be in the majority of cases, is not the only answer since intracranial corticopallidodentate calcification has been reported in patients with no parathyroid deficiency and, on the other hand, a number of patients with conspicuous parathyroid insufficiency have been reported without calcification (6).

Many patients who present with somatic features, the combination of short stature, obesity, round face, brachydactyly (commonly affects 4<sup>th</sup> and 5<sup>th</sup> metacarpal bones) and soft tissue calcification, are distinctive and known as Albright's hereditary osteodystrophy ( AHO) (1,8) as seen in two of our cases.

Presence of hypocalcemia and hyperphosphatemia in the absence of hypomagnesemia or chronic renal failure leads to suspicion of hypoparathyroidism. The differentiation between true and pseudohypoparathyroidism rests on the demonstration of either absence or presence of end organ resistance to the action of PTH. Untreated PHP almost uniformly show elevated serum levels of PTH and in the absence of hypomagnesemia or chronic renal failure, the diagnosis is fairly certain, as in our cases (2).

The bones may appear dense radiographically. In contrast to patients with hypoparathyroidism, pseudohypoparathyroidism patients have evidence of increased bone turnover, with increased urinary excretion of hydroxyproline and reduced bone density and some actually have hyperparathyroid bone disease (7).

**Classification of Pseudohypoparathyroidism (8)****Table 1**

Type	Hypocalcemia, Hyperphosphatemia	Response of Urinary cAMP to PTH	Serum PTH	G <sub>Sα</sub> <input type="checkbox"/> Subunit Deficiency	AHO	Resistance to Hormones in Addition to PTH
PHP-Ia	Yes	decreased	increased	Yes	Yes	Yes
PHP-Ib	Yes	decreased	increased	No	No	No
PHP-II	Yes	Normal	increased	No	No	No
PPHP	No	Normal	Normal	Yes	Yes	±

Pseudohypoparathyroidism-Ia is the most common type (8). Pseudopseudohypoparathyroidism (PPHP) is an incomplete form of pseudohypoparathyroidism marked by the same constitutional features including the phenotypic appearance of PHP – Ia but having normal levels of calcium and phosphorus in the blood serum. Thus 2 of our patients (Cases 2 and 3) were having PHP – Ia while our 3<sup>rd</sup> patient (Case 1) lacked AHO phenotype (2). The long term treatment of hypocalcemia in patients with PHP and PPHP involves administration of oral calcium and vitamin D in doses lower than true hypoparathyroidism (8). The goals of therapy are to maintain the appropriate blood calcium concentration and urinary calcium excretion. In our patients, three months after vitamin D and calcium supplement, the serum calcium and phosphorus levels returned to normal limits and they becoming seizure free.

**CONCLUSIONS**

Children presenting with recurrent seizures and showing bilateral basal ganglia calcification on CT Brain should undergo detailed metabolic investigations. Hypocalcemia, hyperphosphatemia, raised PTH levels and normal renal function on blood investigations and often association with a characteristic constellation of developmental defects (AHO) makes the diagnosis of pseudohypoparathyroidism. Almost all patients of recurrent seizures with PHP can be effectively treated with calcium and vitamin D in addition to the antiepileptic drugs.

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## APPENDICES

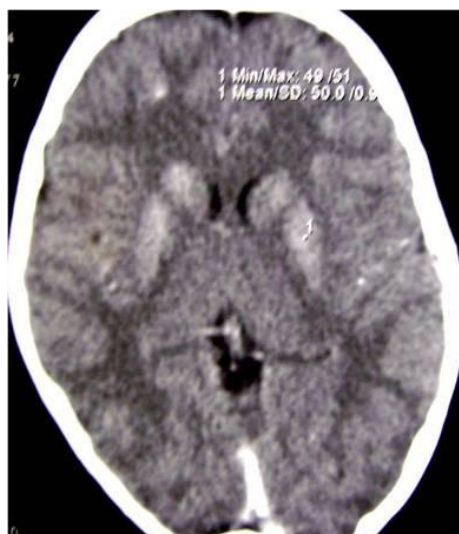


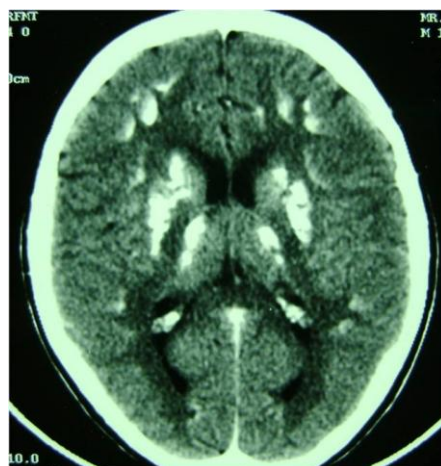
Figure 1



Figure 2



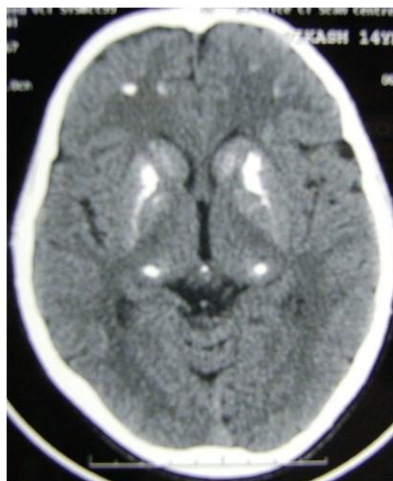
Figure 3



**Figure 4**



**Figure 5**



**Figure 6**